REMARKS

This Amendment responds to the Final Office Action mailed on September 2, 2008. In the Office Action, the PTO:

- rejected claims 13-20, 69-81 and 83-85 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Gosselin *et al.* (U.S. Patent No. 6,444,652) in combination with Weis *et al.* (WO 96/13512).

Claims 13-20, 69-81 and 83-85 are pending. Claims 13 and 17 are amended to delete the terms "optionally" and "if necessary" and to add the recitations that (a) step (d) occurs in chloroform; (b) the ratio of the silylated thymine to the protected L-1-halo-2-deoxyribose is at least 1:1; and (c) the β/α ratio of L-2'-deoxythymidine or L-2'-deoxyuridine is greater than about 10:1. The amendments are supported by the specification, for example, in paragraph [0133] of the specification, i.e., at pages 9-10 of US 2004/0266996 A1. Claim 78 is amended to correct a typographical error. Claim 85 is amended to be consistent with the currently amended claim 13 and to delete the dependency on claim 17. New claim 86 is added to cover the deleted part of currently amended claim 85. Claims 14 and 18 are canceled. No new matter is added by this Amendment. After this Amendment, the pending claims are claims 13-20, 69-81 and 83-86.

Response to Rejections Under 35 U.S.C. § 103(a)

Claims 13-20, 69-81 and 83-85 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Gosselin *et al.* (U.S. Patent No. 6,444,652) in combination with Weis *et al.* (WO 96/13512). Claims 13 and 17 are amended to delete the terms "optionally" and "if necessary" and to add the recitations that (a) step (d) occurs in chloroform; (b) the ratio of the silylated thymine to the protected L-1-halo-2-deoxyribose is at least 1:1; and (c) the β/α ratio of L-2'-deoxythymidine or L-2'-deoxyuridine is greater than about 10:1. Claims 14 and 18 are canceled and therefore, the rejection of claims 14 and 18 is moot.

The instant claims are drawn to processes for the preparation of β-L-2'-deoxythymidine and β-L-2'-deoxyuridine. The PTO alleged that (1) it is proper to combine the teachings of Gosselin *et al.* and Weis *et al.* because the process of Gosselin *et al.* and Weis *et al.* may also yield the α isomer in addition to the β isomer; (2) the process of the cited references allegedly reads on the instant claims since it allegedly produces the required β

nucleoside; and (3) the instant claims allegedly are not drawn to selectivity. See page 4 of the Final Office Action mailed on September 2, 2008.

The current standard of obviousness takes into account (1) whether there would have been a "reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does;" and (2) whether the combination of elements would have yielded "predictable results" *i.e.*, whether there would have been a reasonable expectation of success. (*See e.g., PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d at 1342, 1360 (Fed. Cir. 2007) ("The burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, and would have had a reasonable expectation of success in doing so.") (emphasis added, internal quotations omitted)).

With regard to the instant case, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness. Specifically, Applicant respectfully submits the following:

(1) The cited references would not have provided any reason to select every limitation in either step (c) or step (d) of the processes of claims 13 and 17; and

(2) The cited references would not have provided the legally required reasonable expectation of success.

1. The cited references would not have provided any reason to select every limitation in either step (c) or step (d) of the processes of claims 13 and 17.

The instant claims are not obvious in view of the cited references, Gosselin *et al.* and Weis *et al.*, because the cited references, individually or in combination, do not teach or suggest all the claim elements of the independent claims 13 and 17, as amended. For instance, the cited references do not teach or suggest step (c) or step (d), much less a combination of steps (c) and (d), of the **stereoselective** processes of currently amended claims 13 and 17 that results in a ratio of β-L-2'-deoxythymidine to α-L-2'-deoxythymidine greater than about **10:1**.

Step (c) of the currently amended claims 13 and 17 recites "reacting the protected L-1-O-alkyl-2-deoxyribose with an anhydrous acid halide to form a protected L-1-halo-2-deoxyribose, wherein the anhydrous acid halide is produced *in situ* by the reaction of

an acyl halide with a sub-equivalent amount of a second alcohol." Neither Weis *et al.* nor Gosselin *et al.* teaches, discloses or suggests that an acid halide, such as HCl, can be generated *in situ* from the reaction of an anhydrous acyl halide with a sub-equivalent amount of an alcohol. Weis *et al.* at page 20 merely discloses the reaction between a protected L-1-O-alkyl-2-deoxyribose and dry hydrogen chloride gas in acetic acid. *See* the scheme at page 2358 and Example 17 at page 2366 of the enclosed *Tetrahedron* **Vol. 3**, No. 10, pp. 2355-2368 (1987) which is cited in the second sentence of Step A of Example 25 at page 35 of Weis for making compound 56. Therefore, neither Weis *et al.* nor Gosselin *et al.* provides a reason to modify the use of dry hydrogen chloride gas in acetic acid to an anhydrous acid halide produced *in situ* by the reaction of an acyl halide with an alcohol. Further, under the mild conditions of step (c), the protected L-1-halo-2-deoxyribose crystallizes readily as it forms and thus avoids the usual decomposition observed with other methods, such as that described in Weis *et al.* *See* paragraph [131] of the instant application.

Step (d) of the currently amended claim 13 or 17 recites "coupling the protected L-1-halo-2-deoxyribose with silylated thymine (or uracil) to form a protected β-L-2'-deoxythymine (or deoxyuridine) in chloroform, wherein the ratio of the silylated thymine (or uracil) to the protected L-1-halo-2-deoxyribose is at least 1:1 and wherein the ratio of the protected β-L-2'-deoxythymine (or deoxyuridine) to the protected α-L-2'-deoxythymine (or deoxyuridine) is greater than about 10:1." The instant application in paragraph [133] discloses that the solvent requirement of the coupling step can be strict and chloroform was found to provide unexpected high stereoselectivity. As indicated by the enclosed declaration executed by the Applicant, other solvents tested, including acetonitrile, provided very low levels of stereoselectivity. Weis *et al.* merely discloses the use of acetonitrile in the coupling step. *See* the first sentence of Step A of Example 25 at page 35 of Weis *et al.* Gosselin *et al.* also merely discloses the use of acetonitrile in the coupling step. *See* Schemes in Examples 1-3 in col. 13-14, 17-18, and 25-26. Neither Weis *et al.* nor Gosselin *et al.* provides a reason to substitute the solvent acetonitrile with the solvent chloroform to yield a ratio of the protected β-L-2'-deoxythymine (or deoxyuridine) to the protected α-L-2'-deoxythymine (or deoxyuridine) greater than about 10:1.

2. The cited references would not have provided the legally required reasonable expectation of success.

The Examiner has failed to explain how one skilled in the art would have had a reasonable expectation that the claimed processes would be effective in providing the

claimed selectivity. The Federal Circuit, following *KSR*, articulated guidelines for determining "whether the expectation of success from a particular line of inquiry is great enough to render a resulting invention obvious." (*PharmaStem*, 491 F.3d at 1364). As the Federal Circuit explained:

> [A]n invention would not be invalid for obviousness if the inventor would have been motivated to **vary all parameters or try each of numerous possible choices** until one possibly arrived at a successful result, where the prior art gave either **no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful**. Likewise, an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

(*Id.* (citing *In re O'Farrell*, 953 F.2d 894, 903 (Fed. Cir. 1988))(internal quotations omitted) (emphasis added)).

In the instant case, to arrive at the instant methods, not only would one skilled in the art have had to "try each of numerous possible choices" for, *inter alia*, steps (c), but one skilled in the art would have also have had to "try each of numerous possible choices" for step (d). As discussed earlier for step (c), Weis *et al.* at page 20 merely discloses a hydrogen chloride source from dry hydrogen chloride gas in acetic acid but does not suggest *in situ* reaction between an acyl halide with an alcohol among numerous possible choices of hydrogen chloride source, such as hydrochloric acid or hydrogen chloride gas in numerous possible solvents (*e.g.*, alcohols). Gosselin *et al.* is silent about the use of hydrogen chloride. Further, as discussed earlier for step (d), Weis *et al.* and Gosselin *et al.* merely disclose the use of acetonitrile, not chloroform, among numerous possible choices of solvents for the coupling step. Therefore, none of the cited references would have provided any "indication of which parameters were critical" or any "direction as to which of [the] many possible choices is likely to be successful." As is evident from *PharmaStem*, this scenario is exactly what the Federal Circuit warned is **not** a legally sufficient "reasonable expectation of success." (*Id.*). The combination of references, at most, would have merely provided general guidance and would have merely provided a process of making deoxythymidine or deoxyuridine without any indication as to why the instant conditions in steps (c) and (d) would be specifically useful for the recited stereoselectivity. Thus, the cited references do not provide the requisite expectation of success, and the rejection should be withdrawn.

For the above reasons, Applicants submit that the currently amended claims 13 and 17 and thus claims 15-16, 19-20, 69-81 and 83-85, which depend from claim 13 or 17, are not obvious over Gosselin *et al.* in combination with Weis *et al.* Applicants respectfully request withdrawal of the rejection of claims 13, 15-17, 19-20, 69-81 and 83-85 under 35 U.S.C. 103(a) as being allegedly unpatentable over Gosselin *et al.* in combination with Weis *et al.*

CONCLUSION

In light of the above amendments and remarks, the Applicants respectfully request that the PTO reconsider this application with a view towards allowance.

No fee other than the extension fee is believed due for this submission. However, if any fees are required for the entry of this paper or to avoid abandonment of this application, please charge the required fees to Jones Day Deposit Account No. 50-3013 (referencing order no. 417451-999010).

The Examiner is invited to call the undersigned attorney at (650) 739-3983, if a telephone call could help resolve any remaining items.

Respectfully submitted,

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